PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparative efficacy of treatment strategies for hepatocellular carcinoma: systematic review and network meta-analysis
AUTHORS	Tian, Guo; Yang, Shigui; Yuan, Jinqiu; Threapleton, Diane; Zhao, Qiyu; Chen, Fen; Cao, Hongcui; Jiang, Tian'an; Li, Lanjuan

VERSION 1 – REVIEW

REVIEWER	Wen-Wei, Sung School of Medicine, Chung Shan Medical University, Taichung, Taiwan; Department of Urology, Chung Shan Medical University Hospital, Taichung, Taiwan
REVIEW RETURNED	18-Jan-2018

GENERAL COMMENTS	Congratulation of this work. The topic is clear defined and is important issue especially in Asian country. The data is well summarized and the manuscript is well written. There is no doubt that the authors spare no effort in this work. I also learn a lot about preparing a manuscript from this work. Thank you.

REVIEWER	Jacopo Desiderio St. Mary's Hospital of Terni, Italy
REVIEW RETURNED	20-Jan-2018

GENERAL COMMENTS	This is an excellent work. Particularly the authors have made a huge statistical analysis and developed a good review of current literature.

REVIEWER	RUTH PICKERING UNIVERSITY OF SOUTHAMPTON, UK
REVIEW RETURNED	27-Feb-2018

GENERAL COMMENTS	This paper reports a systematic review and meta analysis of studies examining treatments for hepatocellular carcinoma. The statistical analysis is based on quite complex Bayesian networks. I've got the following specific points to raise. 1 In the Abstract, Results section, page 5, line 30, the direction of the ranking, that is whether high rank indicates greatest of least treatment benefit should be indicated. 2 Study inclusion criteria, page 9, line 28, studies had to report at least two treatment. Were there studies that compared a treatment to control? 3 Study exclusion criteria, page 9, lines 38-43, studies where participants received combinations of the 5 treatments. What if such a study included arms where participants received single

	treatments? Isn't it of interest to look at combination treatments? 4 Data analysis, page 10, line 28, "is a closed evidence loop was available". I think there should be an explanation of what this means. 5 Data analysis, page 9, they describe analyses pooling the odds ratios (though it isn't stated - this is presumably the odds ratio of death/survival within 1 year, 3 years or 5 years of treatment). I would have anticipated the constituent studies to report survival analyses, with some participants not being available for the whole periods and being censored. How were censored observations treated in the analyses of death or not by each follow-up point? 6 Page 9, lines 43-50, the sentence describing Bayesian network analysis. Is this described in reference 16 quoted in the previous sentence? If not there should be a reference describing it. 7 Page 12, line 37, this sentence says that survival probabilities and ranks are displayed in Figures 2-5. The legends to Figures 2 and 3, say that they show numbers of participants and also numbers of studies showing connected treatments, not survival probabilities or ranks. Would it be possible to add the numbers of connected studies to the lines? Also it should be stated in the data analysis section that these plots are going to be presented. 8 Figures 4 and 5 showing the ranks. There isn't much explanation of this, but presumably the number of studies contributing to each time point 1 year, 3 years and 5 years, decreases with time. The mean ranks will depend on the number of studies contributing to the time point, and if this varies over time points it means that the only comparisons that can be drawn are across treatment within a timepoint. It would be more sensible to cluster by time point so that the comparisons across treatments lie adjacent to each other in the plots. The numbers of contributing studies could usefully be given in the figures. 9 Tables 1 and 2. In the titles to these tables it should state that the odds ratios are of survival (not death at 1 year, 3 year and 5 years - if that is the case. Though with the footnote to the table explaining that the reference treatment is to the right hand side in the table, I think it is correctly explained, I did have to spend quite a bit of time working out which way round the odds ratios were presented. The sentence presenting the odds ratios in the Results section, page 13, liens 6-13, was also quite difficult to understand

VERSION 1 – AUTHOR RESPONSE

3.Reviewer: 1
Reviewer Name: Wen-Wei, Sung
Institution and Country: School of Medicine, Chung Shan Medical University, Taichung, Taiwan; Department of Urology, Chung Shan Medical University Hospital, Taichung, Taiwan
Congratulation of this work. The topic is clear defined and is important issue especially in Asian country. The data is well summarized and the manuscript is well written. There is no doubt that the authors spare no effort in this work. I also learn a lot about preparing a manuscript from this work. Thank you.
Response: Thank you for your comment. We will carry on more in-depth studies in the future.

4.Reviewer: 2
Reviewer Name: Jacopo Desiderio
Institution and Country: St. Mary's Hospital of Terni, Italy
This is an excellent work. Particularly the authors have made a huge statistical analysis and developed a good review of current literature.
Response: Thank you for your comment. We will carry on more in-depth studies in the future.

5.Reviewer: 3
Reviewer Name: RUTH PICKERING
Institution and Country: UNIVERSITY OF SOUTHAMPTON, UK
This paper reports a systematic review and meta analysis of studies examining treatments for hepatocellular carcinoma. The statistical analysis is based on quite complex Bayesian networks. I've got the following specific points to raise.
In the Abstract, Results section, page 5, line 30, the direction of the ranking, that is whether high rank indicates greatest of least treatment benefit should be indicated.
Response: Thanks for this suggestion. We have rephrased the sentence as following:" After adjustment for study design, and in the full sample of studies, the treatments were ranked in order of good to bad as follows for 5-year survival: 1) RES, 2) TR, 3) RFA, 4) MWA, and 5) PEI." These could be available in Abstract, Results section of the revised manuscript.

6.Study inclusion criteria, page 9, line 28, studies had to report at least two treatment. Were there studies that compared a treatment to control?
Response: Thanks for this suggestion. In the network analysis, any two treatments of comparisons could be included in the analysis, which did not have to contain a control group in each group. Thus we did not mention it in Study inclusion criteria.

7.Study exclusion criteria, page 9, lines 38-43, studies where participants received combinations of the 5 treatments. What if such a study included arms where participants received single treatments? Isn't it of interest to look at combination treatments?
Response: We appreciated this suggestion. Because single treatment cannot be calculated in the network analysis, we did not include it. What's more, we agree with you, but did not find studies with the combination of the 5 treatments, and thus deleted this sentence in Study exclusion criteria, page 9, lines 38-43. Please see them in Search Strategy of the revised manuscript.

8.Data analysis, page 10, line 28, "is a closed evidence loop was available". I think there should be an explanation of what this means.
Response: We appreciated this suggestion. In this network analysis, studies containing at least two therapeutic ways are included, which could constitute a ring or open loop. Through it we would calculate the results of comparison between any two groups in the networks. We have rephrased the sentence as following:"Network meta-analysis was used if a ring or open evidence loop was available." Please see them in Data Analysis of the revised manuscript.

9.Data analysis, page 9, they describe analyses pooling the odds ratios (though it isn't stated - this is presumably the odds ratio of death/survival within 1 year, 3 years or 5 years of treatment). I would have anticipated the constituent studies to report survival analyses, with some participants not being

available for the whole periods and being censored. How were censored observations treated in the analyses of death or not by each follow-up point?
Response: We appreciated this suggestion. We confirmed that in Data analysis section, we pooled the odds ratios of survival within 1 year, 3 years or 5 years of treatment.For those participants not being available for the whole periods and being censored,we appraised the potential risk of bias for these people lost to follow-up in each study in accordance with GRADE guidance (Table S2).

10.Page 9, lines 43-50, the sentence describing Bayesian network analysis. Is this described in reference 16 quoted in the previous sentence? If not there should be a reference describing it.
Response: We appreciated this suggestion. We checked that the sentence was described in reference 16 quoted in the previous sentence.We have cited reference 16 in the corresponding position. Please see them in Data Analysis of the revised manuscript.

11.Page 12, line 37, this sentence says that survival probabilities and ranks are displayed in Figures 2-5. The legends to Figures 2 and 3, say that they show numbers of participants and also numbers of studies showing connected treatments, not survival probabilities or ranks. Would it be possible to add the numbers of connected studies to the lines? Also it should be stated in the data analysis section that these plots are going to be presented.
Response: We appreciated this suggestion. The numbers of connected studies to the lines and (black) and sample size of each treatment (red) were shown in Figure 2 and 3, respectively. Please see them in Figure 2 and 3 of the revised manuscript.

12.Figures 4 and 5 showing the ranks. There isn't much explanation of this, but presumably the number of studies contributing to each time point 1 year, 3 years and 5 years, decreases with time. The mean ranks will depend on the number of studies contributing to the time point, and if this varies over time points it means that the only comparisons that can be drawn are across treatment within a timepoint. It would be more sensible to cluster by time point so that the comparisons across treatments lie adjacent to each other in the plots. The numbers of contributing studies could usefully be given in the figures.
Response: We appreciated this suggestion. In Figure 2 and 3 in this network analysis,circle size is proportional to the number of included patients and line width indicates the number of studies comparing the connected treatments. We thought that adding this information in Figure 2 and 3 is more appropriate than that in Figures 4 and 5. The numbers of connected studies to the lines and (black) and sample size of each treatment (red) were shown in Figure 2 and 3, respectively. These could be available in Figure 2 and 3 of the revised manuscript.

13.Tables 1 and 2. In the titles to these tables it should state that the odds ratios are of survival (not death at 1 year, 3 year and 5 years - if that is the case. Though with the footnote to the table explaining that the reference treatment is to the right hand side in the table, I think it is correctly explained, I did have to spend quite a bit of time working out which way round the odds ratios were presented. The sentence presenting the odds ratios in the Results section, page 13, liens 6-13, was also quite difficult to understand.
Response: We appreciated this suggestion. We have revised the titles in Table 1 as “Table 1 Odds ratios (95% credible interval) according to network meta-analyses for the survival for all pairwise comparisons in randomized controlled trials.” and Table 1 as “Table 2 Odds ratios (95% credible interval) according to network meta-analyses for the survival for all pairwise comparisons in all studies”. Meanwhile, we have rephrased the sentence in the Results section, page 13, liens 6-13 as following:”Compared to RES, the 5-year survival in all studies (trials and observational studies) for all

tumors ≤5cm, was 0.47 (95%CrI 0.22 to 0.87) for PEI, 0.79 (95%CrI 0.24 to 1.92) for TR, 0.56 (95%CrI 0.23 to 1.14) for MWA and 0.56 (95%CrI 0.27 to 0.99) for RFA (Table 2).” These could be available in Table 1 and Table 2 of the revised manuscript.

In addition, Grammar and syntax have been carefully checked and improved. Other inaccuracies have also been corrected.

VERSION 2 – REVIEW

REVIEWER	RUTH PICKERING University of Southampton, UK
REVIEW RETURNED	09-Apr-2018

GENERAL COMMENTS	several of the points I raised before have been addressed in this revised version. A couple of things could be easily changed 1 Abstract, Results, line 33, it might be better to say in order of greatest to least benefit, rather than from good to bad. The worst treatment seems to be POI - is it fairer to describe it as having least benefit, or is it actually bad, ie worse than nothing. 2 Data analyses section, line 27/8. They should specify that its odds ratio of survival. ie say " ... to calculate the odds ratio (OR) of 1-, 3- and 5-year survival and their 95% confidence intervals." if that is the case. I notice that they haven't addressed my point raised before about the constituent studies possibly conducting survival analysis, taking account of varying lengths of follow-up across participants. I think the statistical methods used will be quite difficult for readers to follow. In the data analysis section there is mention of open evidence loops without explanation of what this means.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3

6. Abstract, Results, line 33, it might be better to say in order of greatest to least benefit, rather than from good to bad. The worst treatment seems to be POI - is it fairer to describe it as having least benefit, or is it actually bad, ie worse than nothing.

Response: Thanks for this suggestion. We have rephrased the relevant sentence as following:” After adjustment for study design, and in the full sample of studies, the treatments were ranked in order of greatest to least benefit as follows for 5-year survival: 1) RES, 2) TR, 3) RFA, 4) MWA, and 5) PEI.” Please see them in the Abstract, Results of the revised manuscript.

7. Data analyses section, line 27/8. They should specify that its odds ratio of survival. ie say " ... to calculate the odds ratio (OR) of 1-, 3- and 5-year survival and their 95% confidence intervals." if that is the case. I notice that they haven't addressed my point raised before about the constituent studies possibly conducting survival analysis, taking a ccount of varying lengths of follow-up across participants.

Response: We appreciated this suggestion. We have rephrased the relevant sentence as folllowing:”When possible, pair-wise direct head-to-head comparisons were conducted to calculate the odds ratio (OR) of 1-, 3- and 5-year survival and their 95% confidence intervals (CI).” For those participants not being available for the whole periods and being censored, we tried to extract data from the figure or table in the article and perform subgroup analysis according to different follow-up lengths (1, 3, 5 years).

8. I think the statistical methods used will be quite difficult for readers to follow. In the data analysis section there is mention of open evidence loops without explanation of what this means.

Response: Thanks for this suggestion. We have rephrased the relevant sentence as following:”Network meta-analysis was used if a ring or open evidence loop was available to know the number of arms and the sample size of each intervention.” Please see them in the Data Analysis of the revised manuscript.